TREATMENT OF IMMUNE DISEASES BY MEANS OF THE ANTIBODY-MEDIATED NEUTRALIZATION OF SPECIFIC INTESTINAL BACTERIA

PRIORITY AND CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is the U.S. National Phase application under 35 U.S.C. § 371 of International Application No. PCT/EP2019/070910, filed Aug. 2, 2019, designating the U.S. and published as WO 2020/025801 A1 on Feb. 6, 2020, which claims the benefit of German Application No. DE 10 2018 213 030.2, filed Aug. 3, 2018. Any and all applications for which a foreign or a domestic priority is claimed is/are identified in the Application Data Sheet filed herewith and is/are hereby incorporated by reference in their entireties under 37 C.F.R. § 1.57.

SEQUENCE LISTING IN ELECTRONIC FORMAT

[0002] The present application is being filed along with an Electronic Sequence Listing as an ASCII text file via EFS-Web. The Electronic Sequence Listing is provided as a file entitled HRZGO01012APCSEQLIST.txt, created and last saved on Feb. 2, 2021, which is 6,246 bytes in size. The information in the Electronic Sequence Listing is incorporated herein by reference in its entirety.

FIELD

[0003] The present invention relates to the treatment of immune diseases and other diseases through the antibody-mediated neutralization of specific intestinal bacteria.

SUMMARY

[0004] The present invention relates to the treatment of immune diseases and other diseases through the antibody-mediated neutralization of specific intestinal bacteria. More particularly, the invention relates to antibody or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment binds to an antigen of the bacterium *Candidatus savagella* and (i) inhibits the adhesion of the bacterium to intestinal epithelial cells, preferably human intestinal epithelial cells, and/or (ii) depletes the bacterium. The invention further provides a drug comprising the antibody according to the invention or an antigen-binding fragment thereof or comprising an antibody which has been produced by the method according to the invention. The invention furthermore relates to a kit comprising an antibody according to the invention or an antigen-binding fragment thereof for reduction of Th17 cell proliferation, Th17 cell differentiation or Th17 cell activity and/or inhibition of the formation of antibodies against endogenous antigens by B cells. The kit according to the invention optionally contains an antibiotic. The invention also provides a method for producing an antibody according to the invention, the method comprising: a) immunizing chickens with an immunogenic peptide from an antigen of the bacterium *Candidatus savagella*; and b) recovering and purifying the antibodies formed in the chickens or in an egg laid by said chickens. The invention lastly relates to a method for producing a drug according to the invention, comprising: a) producing an antibody according to the invention or an antigen-binding fragment thereof; and b) formulating the antibody or an antigen-binding fragment thereof as a drug.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] FIG. **1** shows a graphic summary of an embodiment of the concept forming the basis of the present invention: Specific filamentous *Candidatus savagella* bacteria (segmented filamentous bacteria, SFB) colonize the intestinal wall and, via dendritic cells (DC), activate Th17 cells, which contribute to autoimmunity and atopy. First, suitable bacterial wall proteins of said bacterium are identified (1), synthesized and injected into chickens (2). The chickens form highly specific anti-SFB antibodies, which can be isolated from the eggs (3) and are available for oral antibody therapy in humans (4). A reduction in the SFB microbial count in the intestines can lead to a reduction in Th17 effector cell activity and thus to immunotolerance.

DETAILED DESCRIPTION

[0006] Every person harbors more than 100 trillion bacteria, the entirety of which is referred to as the microbiome. Most of these bacteria colonize the intestines and are useful to humans in the digestion of plant fibers, the provision of vitamins and the displacement of harmful microorganisms. This symbiosis represents a daily test for the human immune system: only a monolayer barrier of epithelial cells separates humans from their microbiome. The immune cells of the intestinal wall constantly have to decide between tolerance to useful bacteria and defense against harmful bacteria. It is therefore not surprising that the composition of the microbiome has a direct and significant influence on the immune system and thus on human health [1].

[0007] In the past few decades, there has been a significant rise in immune-mediated diseases in all industrialized countries. These include the frequent diagnoses of ulcerative colitis, Crohn's disease, rheumatoid arthritis, type 1 diabetes mellitus and multiple sclerosis, but also atopic diseases, such as neurodermatitis and allergic asthma. The rate at which these diseases are increasing is so rapid that genetic changes cannot be the cause. For example, the incidence of allergic asthma in the USA rose by 75% between 1980 and 1994, whereas the incidence in developing countries remained unchanged over the same period [6]. The question that must be asked is what environmental influence can explain this rapid rise in immune-mediated diseases. Altered eating habits, especially the increased intake of salt, fat, sugar and pesticide- and antibiotic-contaminated foods, but also the absence of immunomodulating, parasitic intestinal worms, may cause a disturbed homeostasis between microbiome and immune system (dysbiosis). Other causes of dysbiosis may lie in altered intestinal colonization after birth, for example after caesarean section, and be due to increased hygiene in the living environment. However, the human microbiome has a considerable influence on the manifestation of immune reactions [1]. Certain bacteria which act nonpathologically per se can still have an immunoregulatory or immunostimulating influence. Influencing the microbiome with the aim of therapeutic immunomodulation therefore represents, incidence of selected immune diseases [7], an interesting therapeutic approach for numerous socioeconomically relevant diseases. Although previous approaches such as probiotic [8], prebiotic [9] and antibiotic [10] therapies have been